The foregoing amendments to page 72 of the Specification were made to correct an obvious error in the recitation of the specific number of conservative and non-conservative amino acid differences among the N-terminal 100 amino acid residues of the mature mouse and human OB proteins. More specifically, at page 72, lines 10-13, the specification recites that:

> The N-termini of the mature proteins from both species share even higher homology, with only four conservative and three nonconservative amino acid substitutions among the N-terminal 100 amino acid residues.

However, Figure 4, which provides an alignment and comparison of the mouse and human amino acid sequences, demonstrates that there are in fact six conservative and six non-conservative amino acid substitutions among the N-terminal 100 amino acid residues of the mature mouse and human OB polypeptides. In view of cleavage of the OB polypeptide at the end of the signal sequence, after amino acid Alanine 21 (as detailed in the Specification, including at page 71, lines 14-21), the "N-terminal 100 amino acid residues" of the mature proteins corresponds to amino acids 22-122, starting with V (Valine). The skilled artisan can readily recognize that the mouse and human sequences from 22-122 show six conservative amino acid substitutions (specifically, R-K at 56, S-T at 71, V-I at 85, L-M at 89, L-I at 95 and L-V at 110) and six non-conservative amino acid substitutions (specifically, A-S at 53, Q-R at 92, A-S at 98, S-H at 118, Q-W at 121 and T-A at 122).

Applicants submit that this amendment does not introduce new matter into the specification because the correct conserved and non-conserved amino acid substitutions are readily determined by inspection the sequences presented in Figure 4. Further, Applicants submit that a person of ordinary skill in the art, upon review of Figure 4 and the sequences therein, would readily recognize the error and the correct number of conservative and non-conservative amino acid substitutions in the N-terminal 100 amino acid residues of the mature proteins.

Status of the Claims

Claims 59-65 are pending in the application and stand variously rejected under 35 U.S.C. §112, first paragraph. Applicants traverse these rejections for the reasons indicated herein below and respectfully request reconsideration of the claims 59-65 for allowance.

Objection to the Drawings and Specification

The Examiner objected to the drawings indicating that Figures 8, 11A and 12A were objected to under 37 C.F.R. §1.83(a) for failing to show details described in the specification. Submitted herewith are formal drawings for the instant application. Applicants believe this submission addresses the Examiner's objections to the drawings as well as addressing the points raised in Form PTO-948, which accompanied the Office Action.

The abstract of the disclosure was objected to because it exceeds the 250 word limit. Applicants have amended the abstract to be within the requisite word limit.

The specification was objected to as failing to recite a sequence identifier number at page 76. Applicants present an amendment herein above to rectify this omission.

A marked-up version of the amendments presented herein is provided in Appendix A. Applicants believe the above amendments and submission of formal drawings address the Examiner's objections to the specification, abstract and drawings and request that the objections be withdrawn.

The Claimed Invention is Fully Described in the Specification and the Rejection of the Claims under 35 U.S.C. §112, First Paragraph Should be Withdrawn

Claims 59-65 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse and submit that the claims

of the present invention are fully supported by the written description in the present specification as filed.

Briefly reiterating the rejection, the Examiner suggests that the specification does not provide a written description of the molecules of the claimed invention which "reads on variant OB polypeptides in which amino acids in SEQ ID NO:2, 4, 5 and 6 are substituted with non-conservative amino acids. Applicant claims further read on the variant OB polypeptides having an N-terminal methionine or N-terminal polyaminoacid." (Office Action, paper 8, page 6). The Examiner acknowledges that the specification provides "written disclosure of murine and human ob polypeptides, mature ob polypeptides (cleaved of the signal sequence) and murine and human ob polypeptides lacking glutamine at position 49" (*Id*) but the Examiner goes on to state that the specification does not provide written disclosure of variant Ob polypeptide capable of modulating body weight and contests that Applicants have not adequately pointed out where support exists in the specification for inclusion of substituted OB molecules, the specific amino acids and for non-conservative substitutions recited in the claims. The Examiner further alleges that the specification fails to provide support for OB polypeptides having an N-terminal methionine or an N-terminal polyaminoacid. Applicants respectfully disagree with the Examiner's assertions.

At page 11, line 20 through page 12, line 2, the specification recites that:

> **FIGURE 4** depicts the comparison between the murine (SEQ ID NO:2) and human (SEQ ID NO:4) deduced amino acid sequences. The sequence of the human *ob* deduced amino acid sequence was highly homologous to that of mouse. ***Conservative changes are noted by a dash, and non-conservative changes by an asterisk***. The variable glutamine codon is underlined, as is the position of the nonsense mutation in C57BL/6J ob/ob (1J) mice. Overall, there is 84% identity at the amino acid level, although only six substitutions were found between the valine at codon 22 (immediately downstream of the signal sequence overage) and the cysteine at position 117.

Figure 5 of the application depicts the full length amino acid sequence (SEQ ID NO:5) derived from the murine ob gene that lacks a glutamine residue at position 49, and Figure 6 depicts the full deduced amino acid sequence (SEQ ID NO:6) derived from the human gene but lacking a glutamine residue at position 49. Hence, the specification and at least Figures 4-6 of the application expressly exemplify conservative and non-conservative changes in the amino acid sequence of OB polypeptide between mouse and human sequences. More specifically, Figure 4 provides an alignment of the mouse and human amino acid sequences (SEQ ID NO:2 and 4, respectively) and demonstrates that there are six conservative and six non-conservative amino acid substitutions (indicated by an asterisk) among the N-terminal 100 amino acid residues of the mature mouse and human OB polypeptides (as discussed above). In fact, those of skill in the art reviewing the specification and Figure 4 will readily be able to determine that between the mouse and human sequences there are 28 amino acid substitutions, 19 of which are non-conservative.

It is readily apparent from the specification, including and in particular Figure 4, that as between amino acids 22 and 167 of SEQ ID NO:4 and SEQ ID NO:2, the residues at amino acids 53, 56, 71, 85, 89, 92, 95, 98, 110, 118, 121, 122, 126, 127, 128, 129, 132, 139, 157, 159, 163 and 166 differ. Of these differences, those at residues 53, 92, 98, 118, 121, 122, 126, 127, 128, 132, 137, 159 and 166 are non-conservative substitutions. Similarly, one skilled in the art can readily determine that, as between amino acids 22 and 166 of SEQ ID NO:5 and SEQ ID NO:6, amino acid residues 52, 55, 70, 84, 88, 91, 94, 97, 109, 117, 120, 121, 125, 126, 127, 128, 131, 138, 156, 158, 162 and 165 differ.

It is well established that a claimed invention need not be described *ipsis verbis* in the specification in order to satisfy the requirements of 35 U.S.C. §112. *Ex parte Holt*, 19 U.S.P.Q.2d 1211, 1213 (B.P.A.I. 1991). Applicants submit that the specification as filed, which teaches that non-conservative substitutions are contemplated, including Figures 4, 5, 6

and related sequences, which explicitly recite the positions where such substitutions are desirable, reasonably conveys to one of skill in the art that Applicants were in possession of the subject matter of the claims presently at issue.

Similarly, the specification provides sufficient written description of polypeptides having an N-terminal methionine or an N-terminal polyaminoacid, such that one of skill in the art would appreciate that Applicants had possession of the claimed invention as of the date of filing. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568, 43 U.S.P.Q.2d 1398, 1405 (Fed. Cir. 1997). Moreover, as indicated by the United States Patent and Trademark Office Written Description Guidelines, "[t]he description need only describe in detail that which is ***new or not conventional***." (See 66 FR 1106. Emphasis added). Those of skill in the art at the time the application was filed were aware of techniques for yielding recombinant expression of a peptide or polypeptide. For example, those of skill understood that expression of a given sequence may be facilitated by using an appropriate start signal. The specification, at page 23, lines 3-7, teaches that it is desirable to have:

> ". . . an appropriate start signal (e.g., ATG) in front of the DNA sequence to be expressed and maintaining the correct reading frame to permit expression of the DNA sequence under the control of the expression control sequence and production of the desired product encoded by the DNA sequence."

Those of skill in the art would understand that the codon ATG encodes methionine. Additionally, the specification provides a description of methods and results for achieving expression of "an *ob* fusion with a His tag adopted from the pET expression system under control of the α-mating factor signal sequence. (B) Schematic drawing of the structure of the recombinant ob fusion protein containing a His tag, which includes the α-mating factor signal sequence, putative KEX-2 and STE-13 cleavage sites, the His-tag, and a thrombin cleavage site, and which would yield ob with three surplus N-terminal amino acid residues."

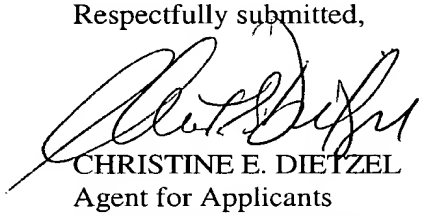
(Specification, page 17, lines 16-22). OB polypeptides generated with other N-terminal amino acids are also discussed in the description for Figure 21, which describes cloning strategies for the recombinant expression of *ob*. From these descriptions, those of skill in the art would recognize that Applicants were in possession of OB polypeptides comprising N-terminal methionine residues and N-terminal polyaminoacid residues.

In light of the above discussion, Applicants submit that the claims of the present invention are fully described in the specification as filed. Applicants, therefore, request that the rejections under 35 U.S.C. §112, first paragraph be withdrawn and the claims be reconsidered for allowance.

Conclusion

The claims as presented herein are believed to be in condition for allowance, and early indication of such a favorable indication is respectfully requested. The Examiner is invited to call the undersigned at the number listed below should the Examiner have any questions or comments relating to this submission.

Respectfully submitted,



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APPENDIX A
MARKED UP VERSION OF AMENDMENTS MADE HEREIN

IN THE SPECIFICATION:

At page 72, please replace the paragraph between lines 1 and 13 with the following rewrittwn paragraph.

-- Human fat tissue RNA was analyzed on Northern blot, RNA species of similar size to the mouse *ob* gene was detected. Sequencing and analysis of cDNA clones revealed that human *ob* also encodes 167 amino acid polypeptide (Figures 2 and 3). Two classes of cDNA with or without three base pairs deletion were found in human as well (Figure 6). The mouse and human *ob* genes were highly homologous in the predicted coding region, but had only 30% homology in the available 3' and 5' untranslated regions. An N-terminal signal sequence was also present in the human *ob* polypeptide. Comparison of the human and mouse *ob* polypeptide sequences showed that the two molecules share an overall 84% identity at amino acid level (Figure 4). The N-termini of the mature proteins from both species share even higher homology, with only ~~four~~ six conservative and ~~three~~ six nonconservative amino acid substitutions among the N-terminal 100 amino acid residues.--

At page 76, please replace the paragraph between lines 17 and 23 with the following rewritten paragraph.

--To establish the relationship between obesity and genetic alterations in the ob gene in humans, the sequence of the human ob gene was determined (FIG. 20A) (SEQ ID NO:22). Specific primers from the human coding sequence were used to screen a human P1 library. Three different P1 clones were obtained, grown up, and PCR amplified using primers flanking the splicing site between the first and second coding exon. The entire intron region, around 2 kB, was amplified and partially sequenced (see FIG. 20A; and as indicated in SEQ ID NO:22).--

IN THE ABSTRACT:

--The present invention relates generally to the control of body weight of animals including mammals and humans, and more particularly to materials identified herein as modulators of weight, and to ~~the~~ diagnostic and therapeutic uses ~~to which such modulators may be put~~ of such modulators. In its broadest aspect, the present invention relates to ~~the elucidation and discovery of~~ nucleotide sequences corresponding to the murine and human *OB* gene, and two isoforms thereof, and proteins ~~putatively~~ expressed by such nucleotides or degenerate variations thereof, that demonstrate the ability to participate in the control of mammalian body weight~~. The nucleotide sequences in object represent the genes corresponding to the murine and human *ob* gene,~~ and that have been postulated to play a critical role in the regulation of body weight and adiposity. ~~Preliminary data, presented herein, suggests that the polypeptide product of the gene in question functions as a hormone.~~ The present invention further provides nucleic acid molecules for use as molecular probes~~,~~ or as primers for polymerase chain reaction (PCR) amplification~~, *i.e.*, synthetic or natural oligonucleotides~~. In further aspects the present invention provides ~~a~~ cloning vectors, ~~which comprises the nucleic~~

~~acids of the invention;~~ and ~~a bacterial, insect or a~~ mammalian expression vectors, ~~which~~ comprising ~~es~~ the nucleic acid molecules of the invention~~, operatively associated with an expression control sequence~~. ~~Accordingly, the~~ The invention further relates to ~~a bacterial or a mammalian cell~~ host cells transfected or transformed with an appropriate expression vector, and their ~~correspondingly, to the~~ use ~~of the above-mentioned constructs~~ in the preparation of the modulators of the invention. Also provided are antibodies to the ob polypeptide. Moreover, a method for modulating body weight of a mammal is provided. ~~In specific examples, genes encoding two isoforms of both the murine and human ob polypeptides are provided.~~